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(54) Title: CRYSTALLINE AMINE SALT OF CEFDINIR

(57) Abstract

Cefdinir in the form of a salt with dicyclohexylamine, a process for its production and its use in the purification of impure cefdinir.

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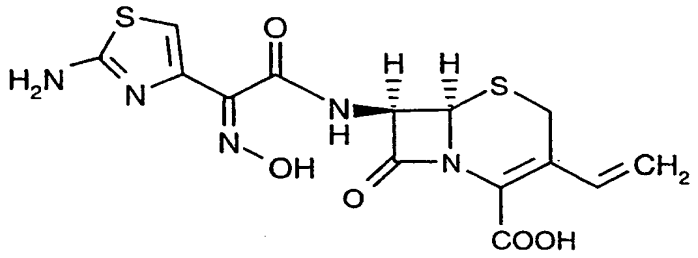
CRYSTALLINE AMINE SALT OF CEFDINIR

The present invention relates to intermediates in the purification of cefdinir, i.e. 7-(Z)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula



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Cefdinir may be used, e.g. in form of a monohydrate, as a pharmaceutical, e.g. antibiotic; see e.g. Y.Inamoto,Toshiyuki Chiba,Toshiaki Kiamimura und Takao Takaya, J.Antibiotics Vol XLI, No 6, 829, (1988).
Cefdinir may be obtained in impure form according to known production processes. It was now surprisingly found that impure cefdinir may be purified via the formation of a salt, e.g. in crystalline form, thereof.

In one aspect the present invention provides a compound of formula I in the form of a salt, e.g. crystalline, with dicyclohexylamine.

A compound of formula I in the form of a salt with dicyclohexylamine may be produced as follows:
Cefdinir, e.g. in the form of a solvate, such as a hydrate, e.g. in impure form, e.g. as obtained in a production process of cefdinir, such as a mixture of cefdinir and impurities, e.g. such as a mixture of by-products originating from the production process of cefdinir and cefdinir; may be treated in the presence of a solvent, e.g. in dissolved or suspended form, with dicyclohexylamine. A solvent includes any solvent which is inert towards cefdinir or towards cefdinir in the form of a salt with dicyclohexylamine, e.g. a polar organic solvent, such as amides, e.g. dimethylformamide; alcohols, e.g. methanol oder ethanol; ketones, e.g acetone; e.g. in combination with water and water. A solvent system, *e.g.* mixtures of individual solvents, *e.g.* as described above may be used. A preferred solvent system may be e.g. acetone/water, including e.g. a ratio of about 100:1 such as 50:1, e.g. 20:1 to 1:5; such as 10:1 to 1:3, e.g. 5:1 to 2:1, e.g. about 1:1. Per equivalent of cefdinir about one equivalent or more, such as 5; e.g. 3, such as 2 equivalents of dicyclohexylamine may be used, e.g. combined

with the mixture of impure cefdinir in a solvent. A compound of formula I in the form of a salt with dicyclohexylamine may crystallize e.g. from a reaction solution, or, e.g. a suspension of a compound of formula I in a solvent may be converted into a crystall suspension of a compound of formula I in the form of a salt with dicyclohexylamine. An anti-solvent may be added to the reaction mixture, e.g. in order to complete crystallization. An anti-solvent includes solvents wherein a compound of formula I in the form of a salt with dicyclohexylamine is insoluble or soluble only to a small extent if added to the solution or suspension of a compound of formula I in the form of a dicyclohexylamine, e.g. apolar solvents; e.g. ethers, such as diethylether, tetrahydrofurane; or a ketone, e.g. acetone. A compound of formula I in the form of a salt with dicyclohexylamine may be isolated from the reaction mixture, e.g. as conventional, e.g. by filtration, centrifugation.

A compound of formula I in the form of a salt with dicyclohexylamine may be obtained in pure form, e.g. in 98% purity and more, such as 99% to 100% purity; e.g. the amount of impurities present in cefdinir in impure form used for salt formation may be decreased; e.g. impurities of 10% and more in cefdinir in impure form may be decreased to impurities of 1% and less, e.g. 0 to 1% in cefdinir in the form of a salt with dicyclohexylamine.
A compound of formula I in the form of a salt with dicyclohexylamine may be further purified by re-suspension or re-dissolution as described above, e.g. in an (anti) solvent (system), e.g. as described above.

In another aspect the present invention provides a process for the production of a compound of formula I in the form of a salt with dicyclohexylamine, e.g. in crystalline form, comprising treating a compound of formula I, e.g. in form of a solvate, such as a hydrate, in a solvent with dicyclohexylamine and isolating a compound of formula I in the form of a salt with dicyclohexylamine, e.g. in crystalline form.

Cefdinir in free form, e.g. in the form of a solvate, such as a hydrate, e.g. monohydrate and in purified form, e.g. in respect with impure cefdinir used for the formation of a salt of a compound of formula I with dicyclohexylamine, may be obtained from a compound of formula I in the form of a salt with dicyclohexylamine, e.g. as conventional for setting free a compound which is in the form of a salt, e.g. in the form of an amine salt; e.g. by adjusting an appropriate pH, e.g. 1.5 to 4, such as 2 to 3; of a mixture, e.g. a solution, of cefdinir in the form of a salt with dicyclohexylamine with a solvent, e.g. in the presence of water, preferably in water, e.g. by addition of an acidic agent, such as an organic or inorganic acid, preferably

an inorganic acid, e.g. sulphuric acid. Cefdinir, e.g. in the form of hydrate, e.g. monohydrate may crystallize and may be isolated, e.g. as conventional, e.g. by filtration, centrifugation.
A compound of formula I may be obtained according to the process of the present invention as such or in the form of a solvate, e.g. a hydrate, e.g. a monohydrate. A compound of formula I obtained according to the process of the present invention as such may be converted into a compound of formula I in the form of a solvate, e.g. a hydrate, such as a monohydrate and vice versa.

In another aspect the present invention provides a process for the production of a compound of formula I, e.g. in form of a solvate, such as a hydrate, e.g. monohydrate comprising converting a compound of formula in the form of a salt with dicyclohexylamine, e.g. in crystalline form, into a compound of formula I, e.g. in the form of a solvate, and isolating a compound of formula I, e.g. in the form of a solvate.

In another aspect the present invention provides a process for the purification of cefdinir in a mixture of a compound of formula I with impurities, comprising forming a salt of a compound of formula I with dicyclohexylamine; and converting a compound of formula I in the form of a salt with dicyclohexylamine, e.g. in crystalline form, into a compound of formula I, e.g. in the form of a solvate, and isolating a compound of formula I, e.g. in the form of a solvate.

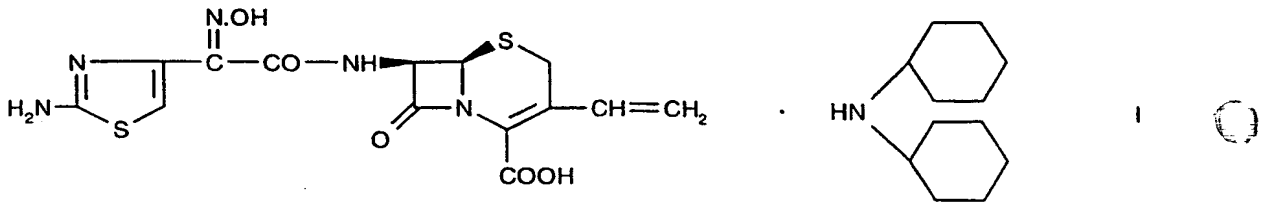
A compound of formula I in the form of a salt with dicyclohexylamine is useful in the purification of cefdinir in impure form.

In another aspect the present invention provides the use of a compound of formula I in the form of a salt with dicyclohexylamine, e.g. in crystalline form in the purification of a mixture of a compound of formula I with impurities.

The present invention has several surprising advantages:
A compound of formula I in the form of a salt with dicyclohexylamine may be in acrystalline form; cefdinir in the form of a salt may be obtained in surprising high purity, e.g. 98% purity and more, e.g. 98% to 100%;- production of the salt is simple; cefdinir obtained from the salt may be surprisingly pure, e.g. 98% and more, e.g. 99% to 100%.

It is surprising that cefdinir under the basic conditions of the salt formation according to the present invention is stable, because from e.g. Yoshihiko Okamoto et al., J. of Pharmaceutical Sciences, Vol 85, No 9, 976, (1996) it is known that cefdinir may be instable in a basic environment; it was e.g. found that cefdinir in the presence of other amines, e.g. tert.-octylamine under similar conditions may be, e.g. heavily, degraded.

In another aspect the present invention provides crystalline 7-(Z)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.dicyclohexylammonium salt of formula



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In the following examples, which illustrate the invention more fully but do in no way limit its scope, all temperatures are given in degrees Celsius. Purity of a compound obtained is determined by HPLC.

Example 1

7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with dicyclohexylamine

10 g of crude cefdinir, e.g. as obtained in a cefdinir production process, in 50 ml of water and 50 ml of acetone are treated under stirring with 5 ml of dicyclohexylamine. A solution is obtained and 7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with dicyclohexylamine crystallizes. 250 ml of acetone are added to the crystall suspension which is stirred for ca. 30 minutes at room temperature. The crystalls are filtrated off, washed with acetone and dried. Crystalline 7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with dicyclohexylamine in a purity of 98.6 % is obtained. Mp: 175° (decomposition).

^{1}H-NMR (DMSO-d_6): 9.41 (d, 1H, J = 8.1 Hz, NH); 7.12 (s, 2H, NH_2); 6.99 (dd, 1H, J = 11.4 and 17.7 Hz, CH = CH_2); 6.64 (s, 1H, thiazol); 5.60 (dd, 1H, J = 4.8 and 8.1 Hz, H_7); 5.15 (d, 1H J = 17.7 Hz, CH = CH_2); 5.04 (d, 1H, J = 4.8 Hz, H_6); 4.94 (d, 1H, J = 11.4 Hz, CH = CH_2); 3.52, 3.39 (AB d, 1H, J = 17 Hz, H_2); 3.21 (m, 2H); 2.05 (m, 4H); 1.8 (m, 4H); 1.6 (m, 2H); 1.2 - 1.4 (m, 10H).

Example 2

7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid in the form of a monohydrate

10 g of 7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with dicyclohexylamine, obtained according to Example 1 are dissolved in 175 ml of water at a temperature of ca. 35-40° and treated with active charcoal. Active charcoal is filtrated off and the pH of the solution obtained is adjusted to pH 2.5 by addition of 5ml of sulphuric acid at ca. 35°. 7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid in the form of a monohydrate precipitates, is filtrated off, washed with water and dried. 7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid in the form of a monohydrate in a purity of 99% is obtained.

Example 3

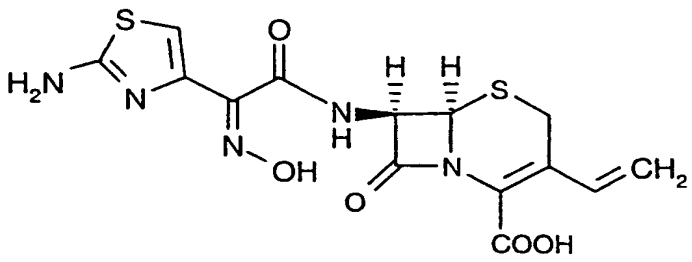
Production of crude cefdinir

40 g of 7-amino-3-vinyl-3-cephem-4-carboxylic acid in 400 ml of dichloromethane are treated with 55.7 ml of N,O-bistrimethyl-silylacetamid. The mixture obtained is stirred for ca. 2 hours at room temperature, cooled to 0° and treated with 52.2 g of 2-(Z)-(2-aminothiazol-4-

yl)-2-acetoxyiminoacetic acid chloride in the form of a hydrochloride in small portions. The mixture obtained is stirred for ca.90 minutes at 0° and added under stirring to a mixture of 44.55 g of $NaHCO_3$, 600 ml of water und 100 ml of dichloromethane of a temperature of 5°. The pH of the mixture obtained is adjusted to a pH of ca. 7.2 - 7.3 with a saturated aqueous solution of $NaHCO_3$. The phases formed are separated. To the aqueous phase 300 ml of water are added and 28.7 g of NH_4Cl. The pH of the mixture obtained is adjusted to pH 8 by addition of an aqueous 10% K_2CO_3 solution and the mixture is stirred for ca. 80 minutes. A solution is obtained. The pH of the solution obtained is adjusted to pH 3 by addition of 5m sulphuric acid. 7-(Z)-[2-(2-amino-thiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid precipitates, is filtrated off, washed with water and dried. 7-(Z)-[2-(2-amino-thiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid in a purity of 94.3 % is obtained.

Patent claims

1. A compound of formula



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in the form of a salt with dicyclohexylamine.

2. A process for the production of a compound of formula I as defined in claim 1 in the form of a salt with dicyclohexylamine comprising treating a compound of formula I in a solvent with dicyclohexylamine and isolating a compound of formula I in the form of a salt with dicyclohexylamine.

3. A process for the production of a compound of formula I as defined in claim 1 comprising converting a compound of formula I in the form of a salt with dicyclohexylamine into a compound of formula I and isolating a compound of formula I.

4. A process for the purification of a compound of formula I as defined in claims 1 in a mixture of a compound of formula I with impurities, comprising
forming a salt of a compound of formula I with dicyclohexylamine; and
converting a compound of formula I in the form of a salt with dicyclohexylamine into a compound of formula I and isolating a compound of formula I.

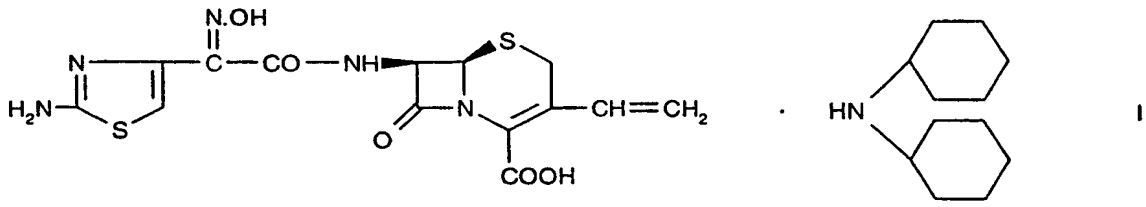
5. A process according to any one of claims 3 to 4 comprising converting a compound of formula I in the form of a salt with dicyclohexylamine into a compound of formula I in the form of a solvate.

6. A process according to any one of claims 3 to 5 comprising isolating a compound of formula I in the form of a solvate.

7. Use of a compound of claim 1 in the purification of a mixture of a compound of formula I with impurities.

8. A compound of formula I as defined in claim I in the form of a salt with dicyclohexylamine according to any one of claims 1 to 7, which is in crystalline form.

9. Crystalline 7-(Z)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.dicyclohexylammonium salt of formula



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A. CLASSIFICATION OF SUBJECT MATTER
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 559 334 A (T. TAKAYA ET AL.) 17 December 1985 see column 2, line 5; claims	1,8,9
Y	WO 97 07121 A (BIOCHEMIE GMBH) 27 February 1997 see page 11 - page 12; claims	1-9
Y	GB 1 038 529 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 10 August 1966 see page 10, example 32; claim 33	1-9
A	EP 0 304 019 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 22 February 1989 see claims	1-9

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[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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P,A	WO 97 24358 A (HANMI PHARMACEUTICAL CO., LTD.) 10 July 1997 see claims	1-9

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